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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,231	02/28/2006	Meng Hsin Chen	21524Y	7529

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EXAMINER	
NOLAN, JASON MICHAEL	
ART UNIT	PAPER NUMBER
1626	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,231	CHEN ET AL.	
	Examiner	Art Unit	
	JASON M. NOLAN	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8* is/are allowed.

6)☒ Claim(s) *1-5,7,11 and 12* is/are rejected.

7)☒ Claim(s) *6,9,10 and 13-16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicants Amendment – After Non-Final Rejection, filed **04/03/2008**. **Claims 1-16** are pending in the instant application; of which, **Claims 6, 9-12, & 15** are currently amended. No new claims are presented.

Response to Arguments

Applicant's arguments filed **04/03/2008** have been fully considered but they are not persuasive. In response to the 112-enablement rejection of **Claims 1-5 & 7** Applicants state: "one of ordinary skill in the art would readily appreciate how to use and make the claimed invention in view of Schemes 1 through 3 and the definition of heterocyclyl and aryl described in the specification." Said response does not clarify how to make and use the invention in the full scope in which it is claimed. One of skill in the art would recognize that the term heterocycle encompasses a plethora of different structures in endless combinations. One of skill in the art would be able to easily envision at least twenty different heterocycles (*see* Spec. p. 8 for an exhaustive list); and, further would acknowledge that the differences in heteroatoms, aromaticity, bonding, and ring size would affect all elements of synthesis, reactivity, and efficacy. For this reason and the reasons disclosed in the Wands analysis herein, Applicants arguments are not convincing.

The 112-indefinite rejection of **Claim 15** is withdrawn per amendment. The 101 & 112 rejection to the "use of" **Claims 9-12** is withdrawn per amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 & 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds wherein the variable **Het/Ar = pyridine**, does not reasonably provide enablement for compounds wherein **Het/Ar = any and/or all C_{6-10} aryl or C_{3-10} heterocycle**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The breadth of the claims - The nature of the invention

Claims 1-5 & 7 are drawn to compounds according to formula I, wherein the definitions of **R_2, R_3, R_4, R_5, R^e, X, Q, Y, Z, etc.** are defined therein. Compounds according to these formulae are potentially useful as pharmaceuticals.

The state of the prior art

A search encompassing the compounds of formula I shows that the art is not so advanced such that the claims can include a scope as broad as **Het/Ar = any and/or all C_{6-10} aryls or C_{3-10} heterocycles**. The Examiner points out that upon review of a comprehensive search, only compounds wherein **Het/Ar = pyridine** (the instant application) are known in the art. Therefore, in order for Applicant to claim any and/or

all C_{6-10} aryls or C_{3-10} heterocycles, there must be guidance (support) in the specification in order to enable one of skill in the art to make and use this invention as claimed.

The level of predictability in the art

The elemental substitution of any aryl or heterocycle for **pyridine** in an organic compound changes the necessary starting materials for making these compounds as well as the reactivity of said starting materials. The elemental difference influences the bond length, electronegativity, and therefore the localization of electrons with respect to the core functionality. Therefore, it is unpredictable to know, from the outlined examples in the instant specification, how to make all of the compounds as claimed in formula I.

The amount of direction provided by the inventor

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to make the claimed compounds commensurate in the scope with the instant claims. There is a lack of information pertaining to the synthesis of any compound according to formula I, except for when **Het/Ar = pyridine.**

The existence of working examples

The working examples set forth in the instant specification are directed to the compounds of formula I, in which **Het/Ar = pyridine**. There has not been provided sufficient evidence that would warrant the skilled artisan to accept the synthetic examples provided in the specification as correlative proof that any compound of formula I would indeed be able to be synthesized using the methods as outlined.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Indeed, in view of the information set forth supra, the instant disclosure is not seen to be sufficient to enable the preparation of any compound of formula I wherein **Het/Ar = any and/or all C_{6-10} aryl or C_{3-10} heterocycle**. One skilled in the art could not use the entire scope of the claimed invention without undue experimentation. One skilled in the art would be confronted with an undue burden of experimentation to acquire alternative starting materials in view of formula I AND attempt to prepare the desired products with no guarantee of success. Furthermore, one skilled in the art would be confronted with an undue burden of experimentation to isolate, characterize, and test the various compounds of formula I.

Claim Rejections - 35 USC § 112

Claims 11 & 12 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for a method of treating ocular hypertension, glaucoma, and other eye disorders, does not reasonably provide enablement for the treatment of the diseases encompassed within instant **Claims 11 & 12**, (i.e. Alzheimer's, diabetes, etc.). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The nature of the invention

The nature of the invention in **Claims 11 & 12** is a method of using the compounds of formula I for the treatment of disorders involving the blocking of maxi-K channels. Further, **Claim 11** includes the prevention of repolarization or hyperpolarization of a mammalian cell.

The state of the prior art and the predictability or lack thereof in the art

The review by Wiederholt *et al.* (*Progress in Retinal & Eye Research* **2000**, *19(3)*, 271-295) establishes that potassium channel blockers are among the most important channels regulating membrane voltage - an important pathway for managing ciliary muscle contractility (p. 281). Ciliary muscle tone is responsible for the regulation of intraocular pressure (p. 272). Therefore, there is evidence to suggest that the instant compounds, which are useful at blocking maxi-K channels, may be useful for the treatment of disorders mediated via such a biological pathway. However, there is not enough evidence provided that would support the claims that same compounds would be useful for the treatment of other diseases such as Alzheimer's disease, depression, cognitive disorders, and/or arrhythmia disorders. Further, although the compounds may be useful for treating repolarization or hyperpolarization of a mammalian cell, it does not mean that the compounds would prevent the repolarization or hyperpolarization of the same cells. For instance, once a mammalian cell is treated with a compound of formula I, and the repolarization or hyperpolarization is thwarted, does it mean that the cell will never be subject to repolarization or hyperpolarization again? Prevention implies that once a cell is treated with a compound of formula I that it will forever be protected

against repolarization or hyperpolarization. There is insufficient evidence that guarantees this from happening.

The state of the prior art, namely pharmacological art, involves screening *in vitro* and *in vivo* to determine if the compounds exhibit desired pharmacological activities, which are then tested for their efficacy on human beings. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. *In the instant case,* the claimed invention is highly unpredictable since one skilled in the art would recognize that a group of compounds and composition, with the ability to block the maxi-K channel, may treat certain diseases related to ocular pressure, but it does not mean that the same group of compounds and compositions may treat other types of diseases, such as Alzheimer's disease or diabetes because those diseases are currently treated with drugs acting via distinct biological pathways from the instant compounds.

The amount of direction or guidance present and the presence or absence of working examples

The direction or guidance present in Applicants' Specification provides evidence that establishes the compounds of the present invention as inhibitors of the Maxi-K channel, (specification pages 42-45). There are no *in vivo* studies; therefore, one of ordinary skill in the art would have to rely on the prior art in order to establish the types of diseases supported by this class of compounds.

The breadth of the claims, quantity of experimentation, and level of skill in the art

Claims 11 & 12 are drawn to a method of treating a plethora of diseases. In order to treat a disease, one would need to demonstrate what the subject population is, what the necessary dose is for efficacy and that the subject has recovered from such a disease. It has only been established that the instantly claimed compounds are enabled to treat ocular diseases. Because of the aforementioned reasons, a person of skill in the art could not practice the claimed invention herein, or a person of skill in the art could practice the claimed invention herein only with undue experimentation and with no assurance of success.

Claim Objections

Claims 6, 9, 10, & 13-16 are objected to as being dependent upon a rejected base, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jason M. Nolan, Ph.D.** whose telephone number is **(571) 272-4356** and electronic mail is Jason.Nolan@uspto.gov. The examiner can normally be reached on Mon - Fri (9:00 - 5:30PM). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph M^{c}Kane** can be reached on **(571) 272-0699**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Jason M. Nolan, Ph.D./

Examiner, Art Unit 1626

/Joseph K McKane/

Supervisory Patent Examiner, Art Unit 1626